DAIDS
Bethesda, MD USA

POLICY

Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements

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CHANGE SUMMARY NOTE: This policy has been reviewed for accuracy and updated to meet 508 compliance guidelines. This version adds a request for site procedures in the event of the death of a parent or legal guardian. This version supersedes version 1.0 dates 24 JUL 2009.

1.0 PURPOSE

The purpose of this policy is to identify written policies and procedures required at all National Institute of Allergy and Infectious Disease (NIAID) Division of AIDS (DAIDS) -supported and/or -sponsored clinical research sites enrolling children in research so as to ensure that research with children is conducted in accordance with applicable U.S. Federal and State regulations and local laws and regulations. Local laws and regulations include those laws applicable in the country or jurisdiction where the research is conducted.

2.0 SCOPE

This policy applies to all clinical research sites sponsored by NIAID (DAIDS) or participating in NIAID (DAIDS) -supported and/or -sponsored clinical research that intend to enroll children (including adolescents) in clinical research.

3.0 BACKGROUND

NIAID (DAIDS)-supported and/or -sponsored clinical research may involve children in the U.S. and, increasingly, children who reside in international settings. U.S. Federal regulations governing research in human subjects identify children as a vulnerable population and mandate additional scrutiny and protections prior to their involvement in research (45 CFR 46, subpart D and, when applicable, the U.S. Food and Drug Administration (FDA) regulations, including 21 CFR 50, subpart D). Local laws, regulations and customs regarding the age to give consent, circumstances under which children may act as adults and identification of responsible persons for children without parents vary from place to place.

A significant portion of NIAID (DAIDS)-supported and/or -sponsored clinical research includes multi-center and network studies requiring centralized development of study (protocol) documents that are subsequently reviewed by multiple Institutional Review Boards (IRBs)/Research Ethics Committees (ECs) at diverse institutions. In order to ensure that NIAID (DAIDS)-supported and/or -sponsored clinical research is in compliance with all applicable laws and

regulations governing the enrollment of children, DAIDS has established requirements for protocol content and requirements for clinical research sites to maintain written site policies and procedures. This policy describes the required site policies and procedures. A companion policy, Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements describes protocol document content requirements and the responsibilities of the Protocol Team, IRB/EC, Clinical Research Site leader (CRS Leader), and Principal Investigator (PI).

4.0 DEFINITIONS

For definitions, see DAIDS glossary.

5.0 RESPONSIBILITIES

Protocol Team

The *Protocol Team* is responsible for providing sufficient detail in the protocol document to allow for the performance of a risk/benefit analysis and an assessment of the need for child assent.

IRB/EC

An *IRB/EC* identified on the Federalwide Assurance of the institution that is engaged in the research is responsible for the review of all clinical research enrolling children, and determining that all of the regulatory requirements are satisfied, including that risks to the child-participants are reasonable in relationship to anticipated benefits [45 CFR 46.111 and Subpart D; 21 CFR 50, subpart D, 21 CFR 56.109; 21 CFR 56.111(2)] and that there are adequate provisions for soliciting the assent of the child and permission of child-participants' parents or guardians [45 CFR 46.408 and 21 CFR 50.55]. The IRB/EC is responsible for determining when each child or all children are capable of assent, whether and how assent must be documented, and when assent is not necessary or can be waived [45 CFR 46.408 21 CFR 50.55].

CRS Leader

The *CRS Leader* is responsible for ensuring that written policies and procedures are developed and maintained at the clinical research site that ensure that the enrollment of children into clinical research is consistent with applicable laws and regulations regarding initial and ongoing parental or guardian permission and child assent, that such procedures are in compliance with local institutional and IRB/EC policies and procedures, and that they are consistently applied.

Principal Investigator

The *Principal Investigator* is responsible for ensuring that DAIDS is informed of the IRB/EC determinations including risk/benefit analysis, IRB/EC approval of studies and amendments, and decisions regarding the need for child assent. The Principal Investigator is also responsible for the following activities:

Conducting the clinical research in accordance with the requirements or determinations of the IRB/EC;

Obtaining and documenting parental/guardian permission and child assent prior to the child's participation in the research, unless these requirements have been waived by the IRB/EC;

Obtaining prior approval from the IRB/EC for any modifications of the previously approved research, including modifications to the parental/guardian permission and child assent process and document, except those necessary to eliminate apparent immediate hazards to the child-subjects;

Ensuring that progress reports and requests for continuing review and approval are submitted to the IRB/EC in accordance with the policies, procedures, and actions of the IRB/EC;

Prompt reporting to the IRB/EC of any unanticipated problems involving risks to subjects or others;

Prompt reporting to the IRB/EC of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB;

Keeping certain records as required by the HHS and FDA regulations for at least three years after completion of the study.

Clinical Investigator

Clinical investigators are responsible for conducting the clinical research in accordance with the requirements or determinations of the IRB/EC.

6.0 POLICY

6.1 Required Policies and Procedures

Clinical research sites planning or conducting clinical research with children, including adolescents, are required to develop, maintain, and adhere to written policies and procedures that:

6.1.2 Direct site activities related to IRB/EC review and approval of research involving children;

6.1.3 Direct activities related to the identification and enrollment of children;

6.1.4 Identify appropriate procedures for obtaining and documenting parental/guardian permission and child assent; and

6.1.5 Identify appropriate procedures detailing site actions related to children enrolled in any study in the event of the death of a parent or legal guardian.

In some cases, clinical research sites with a predominantly adult clinical research focus will appropriately seek to enroll adolescents for whom the research is scientifically relevant and ethically appropriate; the specific criteria for enrollment of adolescents would be specified in the protocol. These sites are encouraged to also develop and maintain written policies and procedures to expedite enrollment of eligible adolescents into adult-oriented clinical research.

6.2 The clinical research site's written policies and procedures for enrollment of children may be an institutional policy and procedure, IRB/EC policy and procedure, clinical research site policy and procedure, or a combination of the above. Policies and procedures developed at the clinical research site level must be submitted to the IRB/EC for review and written approval.

6.3 All clinical research site policies and procedures must be consistent with the requirements of 45 CFR 46 and any other applicable U.S. Federal, State, or local laws; National Institutes of Health (NIH), NIAID, or DAIDS policy.

6.4 Circumstances of a specific clinical research project may require the development of unique policies and procedures for the enrollment of children that are in addition to or supersede standard institutional, IRB/EC, or clinical research site policies and procedures. These policies must be consistent with 45 CFR 46 and, for FDA regulated research, with 21 CFR Parts 50 and 56 as well as any other applicable U.S. Federal, State, or local laws.

6.5 IRB/EC Risk/Benefit Assessment

U.S. Federal regulations [45 CFR 46, subpart D & 21 CFR 50, subpart D] require IRB/ECs to determine whether a proposed study involving children is more than minimal risk; whether there is a potential for direct benefit to participants; and, for studies considered to be greater than minimal risk, whether the study is likely to generate generalizable knowledge. The outcome of these determinations places the research into one of the four regulatory categories identified below, each of which has important implications for study approval and need for additional protections.

6.5.1 45 CFR 46.404: Research not involving greater than minimal risk

21 CFR 50.51: Clinical investigations not involving greater than minimal risk

6.5.2 45 CFR 46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

21 CFR 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

6.5.3 45 CFR 46.406: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition.

21 CFR 50.53: Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition.

6.5.4 45 CFR 46.407: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (This category requires a special level of Department of Health and Human Services (DHHS) review beyond that provided by the IRB/EC.)

21 CFR 50.54: Clinical investigations not otherwise approvable which present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (This category requires a special level of FDA review beyond that provided by the IRB/EC.)

Therefore, all clinical research sites conducting clinical research with children must have procedures in place to ensure that:

6.5.5 Designated clinical research site personnel and the PI are informed in writing of the results of the IRB/EC deliberations.

6.5.6 Written determination of risk/benefit category as described in 6.5 above is maintained in the clinical research site essential documents file.

6.5.7 Protections required by the IRB/EC assessment and decisions are implemented.

6.5.8 Documentation of the IRB/EC decisions is forwarded to the Protocol Registration Office at DAIDS at the time of initial study registration, annual review, and review of amendments and letters of amendment. DAIDS requires submission of the documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404-407 or 21 CFR 50.51-54, and IRB/EC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the PI.

6.6 Guardian Permission

Clinical research sites conducting clinical research with children may wish to include children for whom one or both parents are unable to provide permission due to the parent(s) being dead, unknown, not readily available, or not competent. In these circumstances, federal regulations allow a guardian to provide permission for the child to participate or continue participation in the research.

In anticipation of such circumstances, clinical research sites planning or conducting clinical research with children must have written procedures describing the local standards identifying who may serve as *guardian* [45 CFR 46.402(e) and 21 CFR 50.3(s)].

6.6.1 In countries where the local legal standards for guardianship exist

In countries where the local legal standards for guardianship are *clearly defined*, the clinical research site procedures will include a description of the circumstances under which family and non-family members assume guardianship, as authorized under local law or legal actions required to obtain guardianship, and required documentation, if any.

In countries where the local legal standards for guardianship are *vague*, the clinical research site procedures will include an explanation of the process to identify a guardian. The sponsor or its designee will obtain a definitive interpretation of the applicable

law respecting the identification and appointment of a guardian in the jurisdiction where the research will be conducted from an authorized government official or agency.

6.6.2 In countries where the local legal standards for guardianship do not exist

In countries where the local legal standards for guardianship are *absent*, the clinical research site procedures will include an explanation of the process to identify a guardian. The sponsor or its designee will obtain an affirmative statement from a governmental official or agency with the authority to approve a customary process for identifying and appointing a guardian in the jurisdiction where the research will be conducted.

6.6.3 Other considerations related to guardian permission

Written procedures may also include:

6.6.3.1 What documentation will be required for recognition of such guardianship, if any;

6.6.3.2 How guardianship disputes will be handled for purposes of a child's participation in research.

The site's procedures for recognizing guardianship should be based on applicable local law, regulation, or government policy, where available. Development of the site's written procedures may require consultation with relevant government authorities to ensure accuracy and clarity in the interpretation and application of these guardianship standards.

In all cases, the written procedures for recognizing guardianship should document the source of information or authority relied upon, and justify the reasonableness of such reliance (e.g., why an informal government policy is the most appropriate standard for

recognizing guardianship in this context, or how local custom was validated and assessed). The procedures should be updated as needed to reflect potential changes in applicable legal standards.

6.7 Other Circumstances

Under some circumstances, individuals who would not normally be able to give their consent may provide their own consent, depending on the jurisdiction of the research. For example, in some states, adolescents who consent to their own medical care in certain settings are not considered children under 45 CFR 46, subpart D. The site's policies and procedures must specifically incorporate the following information and the source of the information (local laws):

6.7.1 The legal age for consent to treatments or procedures involved in clinical research, under the applicable law of the jurisdiction in which the research will be conducted.

6.7.2 The legal age for consent to participate in research if the jurisdiction in which the research will be conducted has such laws or regulations.

6.7.3 Age and circumstances (such as marriage and pregnancy) under which individuals are permitted to act independently.

6.8 Waiver of parental/guardian permission

Under some circumstances, the HHS regulations allow the IRB/EC to waive the requirement to obtain parental/guardian permission. In addition to the provisions for waiver under Subpart A [45 CFR 46.116(c) & (d)], if the IRB/EC determines that the research protocol is designed for conditions or for a subject population for which parental/guardian permission is not a reasonable requirement to protect subjects [45 CFR 46.408(c)] (for example, neglected or abused children), the IRB/EC may the waive the requirement to obtain parental/guardian permission, provided an appropriate mechanism for protecting the child- participants is substituted. The waiver must be consistent with Federal, State, or local

law. Clinical research sites may anticipate the need to request waiver of parental/guardian permission for individual children or groups of children and develop written procedures based on IRB/EC requirements and applicable laws and regulations.

NOTE: The provisions for waiver of parental/guardian permission in FDA regulated clinical investigations are limited to 21 CFR 50.23, Exception from General Requirements and 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research.

6.9 Waiver of documentation of parental/guardian permission

Under some specific circumstances, the HHS regulations [45 CFR 46.117(c)] allow the IRB/EC to waive the requirement to obtain a signed parental/guardian permission form. Clinical research sites may anticipate the need to request waiver of documentation of parental/guardian permission for some or all child-participants and develop written procedures based on IRB/EC requirements and applicable laws and regulations.

NOTE: Studies that are subject to FDA regulation are not eligible for a waiver of documentation of parental/guardian permission unless they meet the criteria at 21 CFR 50.27 or 21 CFR 56.109(c).

6.10 Assent Procedures

All NIAID (DAIDS)-supported and/or -sponsored clinical research sites planning to enroll children in clinical research must have a written policy and procedure for the assent of children that is in compliance with applicable U.S. Federal regulations [45 CFR 46, subpart D and 21 CFR 50, subpart D] and any other applicable Federal, State, and local laws and regulations. Determining whether eligible children are likely to be capable of providing assent based on the age, maturity, and psychological state is a responsibility of the IRB/EC. At the time of IRB/EC review, the IRB/EC may determine that all, some, or none of the children may be able to provide assent. The clinical research site's written procedure for assent must include the process that will be followed for determining and

documenting whether individual children are capable of providing assent, the content and procedure for assent, and that such assent was obtained, based on the IRB/EC's determinations for obtaining assent.

6.11 Durability of Consent or Permission

Clinical research sites must have written procedures for each protocol to ensure that legally effective consent is maintained and to determine when re-consent should be sought. For example, the IRB/EC may require that re-consent be sought when there is a change in the person(s) who serves as guardian or when a participant reaches legal age of consent or is emancipated for other reasons. There must be procedures in place to ensure that the authorized person provides permission in cases where the IRB/EC requires re-consent of participants or parental permission.

6.11.1 Children who reach the legal age of consent

Clinical research sites should have a written policy that addresses the actions to take when children reach the legal age of consent during their participation in the research. The policy should describe whether a new consent process will be conducted with the now-adult participant, for example, in cases where there are ongoing interactions or interventions with the participants. Note that when a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age to consent to the procedures involved in ongoing research, the now-adult's participation in the research is no longer regulated by the requirements of Subpart D regarding parental or guardian permission and participant assent. (See OHRP FAQs on Research with Children and DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements.)

6.12 Protections for Wards

Subpart D mandates additional protections for children who are wards of the State or any other agency, institution, or entity. Such children can be enrolled in clinical research approved under sections 45 CFR 46.406 and 21 CFR 50.53, or 45 CFR 46.407 and 21 CFR 50.54 only if the research is either

a) related to their status as wards or b) conducted at a location in which most of the children enrolled as subjects are not wards.

6.12.1 To enroll children who are wards into NIAID (DAIDS)-supported and/or -sponsored clinical research that is approved under category 45 CFR 46.406 or 46.407 and 21 CFR 50.53 or 50.54, the site must have written procedures to facilitate and document the recognition of the status of an individual child as a ward and ensure communication of that status to the responsible IRB/EC.

6.12.2 The designated IRB/EC must have written policies and procedures consistent with the applicable regulations (45 CFR 46.409 and 21 CFR 50.56) to determine the requirement for and appointment of an advocate. These requirements must include that:

6.12.2.1 An advocate must be an individual who has the background and experience to act in, and agrees to act in and represent, the best interests of the child for the duration of the child's participation in the research. (An individual may serve as advocate for more than one child.)

6.12.2.2 The advocate must not be associated in any way (except in the role as advocate or member of the IRB/EC) with the research, the investigator(s), or the guardian organization.

7.0 REFERENCES

Code of Federal Regulations, Title 45 CFR Part 46 Protection of Human Subjects

Code of Federal Regulations, Title 45 CFR 46, subpart D, Additional Protections for Children Involved as Subjects in Research

Code of Federal Regulations, Title 21 CFR Part 50 Protection of Human Subjects

Code of Federal Regulations, Title 21CFR Part 50, subpart D, Additional Safeguards for Children in Clinical Investigations

21 CFR 56, Institutional Review Boards

Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors: Process for Handling Referrals to the FDA: Additional Safeguards for Children in Clinical Investigations

Office for Human Research Protections (OHRP) FAQs on Research with Children

Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process. May 26, 2005 Guidance

DAIDS Policy for Enrolling Children (including Adolescents) in Clinical Research: Protocol Document Requirements

8.0 INQUIRIES

Questions and comments regarding this SOP may be directed to the OPCRO Policy Group.

9.0 AVAILABILITY

This policy is available electronically on the Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures webpage.

10.0 APPENDICES

Appendix 1 Risk/Benefit Categories
Appendix 2 Examples of Template Language
Appendix 3 Wards
Appendix 4 Waivers of Parental/Guardian Permission or Child Assent

11.0 APPROVAL

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